Combined Effects of Noise and Ototoxic Drugs

by Stephen A. Falk, M.D.*

Introduction

Although the treatment and rehabilitation of the hearing handicapped have reached highly sophisticated levels, man should not be overly impressed with his achievements. Two recently recognized causes of deafness are a result of our mechanized and "advanced" society. In nature sounds occurring louder than 100 decibels (dB) are a rarity; such intensities when frequently presented to the hearing mechanism can literally be deafening. Man in his industrial society has become more adept than nature in producing noises that are louder and last longer. The attitude that noise is the "price of progress" is a poor reason for condoning its damaging effects. Side effects of modern drug therapy have resulted in an iatrogenic etiology of deafness.

Ototoxicity of noise has been intensively studied for 80 years and of drugs for approximately 20 years, but in contrast to the rather extensive research that has been done on their separate effects, their effects in combination have received little attention. As noise has become almost ubiquitous and as the use of ototoxic drugs increases, chances for their interaction are greater. The effects of both agents when simultaneously present deserve careful study so that appropriate precautions may be taken to prevent

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what damaging effects they exert. A brief discussion of the sources of noise pollution in our environment and the number of people exposed to each agent alone would help in arriving at an estimation of the numbers in our society exposed to both agents.

As society becomes more technologically advanced, the sources of noise pollution are rapidly increasing. However, the problem of e cessively loud and annoying sounds is not new. Roman law forbade the use of chariots beyond late evening because of the noise produced as the metal wheels contacted the cobblestone roads. Queen Elizabeth I did not allow the beating of one's wife after late evening as the consequent and often incessant sobbing disturbed the sleep of citizens. Sources of noise pollution such as aircraft, construction equipment including bulldozers and jack hammers, road traffic, and industrial operations have attracted much attention and pose a threat to hearing and a nuisance to large numbers of people. Studies of men with a history of army combat have amply attested to the deafening effects of gunfire. More recently, attention has been given to the deleterious effects of recreational noise. Acute exposure to sounds from rock'n roll music (1-4), model airplanes, firearms used for sport, firecrackers, toy guns (5), and snowmobiles (6) produces a temporary elevation of hearing threshold. Chronic exposure to some can cause permanent hearing loss.

With such a variety of places exposed to excessive sound—at recreation, at home, on

the streets, and at work—many people are exposed at times to sounds greater than 80 dB(A), a level above which sensorineural hearing loss will occur if exposure continues for many years. Fifty to sixty percent of all industrial workers are exposed to 85 dB or more eight hours of each working day or about 25% of their working lives (7). Considering this group alone, no less than 6 million people, but possibly as many as 16, are exposed to dangerous noise levels (8). Such a large populace is exposed despite the Occupational Safety and Health Act of 1970* which was designed for hearing conservation for industrial workers. To this figure can be added at least 10 million more of urban dwellers who in cities like New York are often exposed to ambient noise levels of 85 dB (9). As suggested later, noise levels lower than 80 dB(A)† may be detrimental if there is co-exposure to drugs. This would involve even more people as potential risks. Finally, if we consider the use of aspirin, just one of the many ototoxic drugs, of which Americans consume nearly 20,000,000,000 tablets yearly (10) (or 100 tablets per person), it becomes evident that millions in our population are exposed to combinations of damaging noise and ototoxic drugs.

Before discussing the combined ototoxic effects of noise and drugs, a review of the pathological, physiological, and functional abnormalities resulting from each follows. By noting the noxious characteristics which these agents have in common, we can arrive

at a better understanding of the possible mechanisms for any combined effect—whether additive, potentiative, or protective.

Noise-induced Ototoxicity

Hearing loss from noise is of two types. In acoustic or blast trauma, noise greater than 140 dB can produce a conductive hearing loss secondary to tympanic membrane rupture and ossicular chain discontinuity and a sensorineural loss from rupture of Reissner's membrane. Noise-induced hearing loss is a more subtle sensorineural deficit, requiring years to develop. This discussion will be concerned with the latter, and reference can be made to the transverse section of a guinea pig cochlea in Fig. 1 and to the diagrammatic representation of an outer hair cell (OHC) in Fig. 2.

In 1890, Habermann made the first clinicopathological correlation between deafness from industrial noise exposure and destruction of the cochlea (11). Studying the temporal bones of a deaf metal worker who was killed by a train he did not hear, Habermann correlated the man's known high frequency sensorineural hearing loss with pathological changes in the organ of Corti. The changes consisted of loss of hair cells, neurons, and spiral ganglion cells more pronounced in the basal turns. Further studies in both the clinic and laboratory have documented the relationship between frequency, intensity, duration, and temporal pattern of noise and subsequent pathology of the cochlea and hearing loss.

The characteristics of noise exposure that will result in permanent damage to the organ of Corti are shown in Fig. 3. The points represent permanent injury in the form of hair cell destruction and/or permanent threshold shifts as assessed by behavioral audiometry. Certain trends in the noise characteristics that produce damage are evident. As the sound pressure level is increased, a shorter duration of exposure is required. Conversely, as the animal is exposed over a longer time, the sound pressure level may be reduced and still result in a similar damage.

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*This legislation set the upper limits of permissible exposure at 90 dB(A) for an 8-hour working day, 95 dB for 4 hours, 100 dB for 2 hours, and up to 115 dB for 15 minutes. However, 15% of people exposed at these maximal limits will develop sensorineural hearing loss. Thus, in theory the Act fails to protect a significant number of industrial workers.

†The A after the dB (decibel) indicates that the sound level was obtained by using a filter which selectively discriminates against low frequencies. The resulting A- weighted sound level correlates best with the ability of the sound to produce hearing loss.
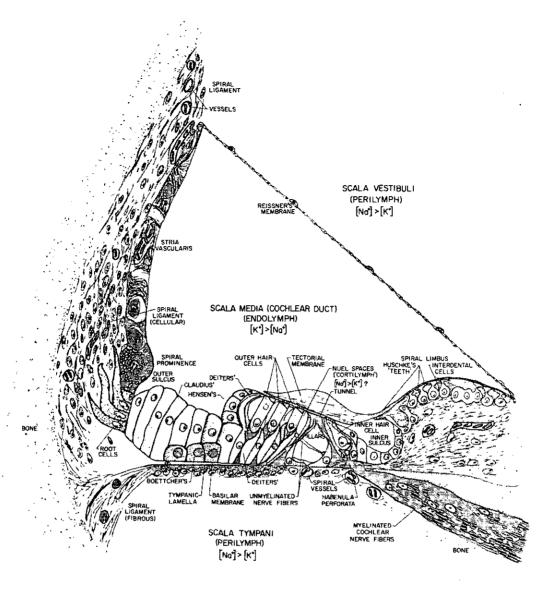
FIGURE 1. - Transverse section of one turn of a guinea pig cochlea. The basilar membrane stretches from the bony shelf near the center of the cochlea to the spiral ligament which with the stria vascularis makes up the outer wall of the cochlea. Reissner's membrane attaching to the top of the stria vascularis and the spiral limbus completes the cochlear part of the membranous labyrinth, a closed tube continuous with the saccule, utricle, three semicircular canals, and endolymphatic duct and sac. Resting on the basilar membrane is the organ of Corti, consisting of outer and inner hair cells, highly specialized supporting cells (pillars, Deiters', Hensen's), and the terminal axons of the cochlear nerve. Not shown are the spiral ganglia located near the center of the cochlea and containing the cell bodies of the cochlear nerve fibers. Note the spiral vessels in the basilar membrane which provide much of the oxygen supply to the organ of Corti. The tectorial membrane provides the shearing force for the bending of stereocilia. The perilymphatic space borders the membranous labyrinth on two sides. It consists of the scala vestibuli, continuous with the vestibule into which the stapes footplate rests in the oval window, and the scala tympani which blindly ends at the round window. These two scalae are continuous at the apex of the cochlea. The membranous labyrinth contains endolymph with composition similar to intracellular fluid and the perilymphatic space contains extracellular-like perilymph (30).
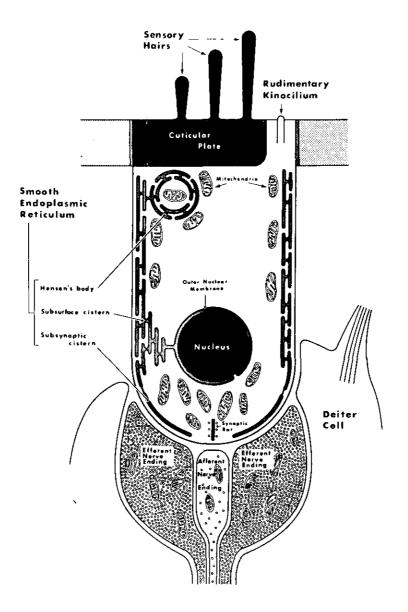
FIGURE 2. - The outer hair cell with its cytoplasmic organelles. The sensory hairs (stereocilia) are attached to the cuticular plate. Note the smooth endoplasmic reticulum complex consisting of Hensen's body (a specialized Golgi apparatus surrounded by mitochondria) and subsurface and subsynaptic cisternae. The smooth ER is continuous with the outer nuclear membrane. The afferent and efferent nerve endings join the outer hair cell at its base (19).

For instance, exposure of the guinea pig to 135 dB noise for 1 minute and to 115 dB noise for 3 hours both produce permanent damage.

In adult humans, approximately 80 dB(A) is the maximal sound intensity unable to produce sensorineural hearing loss regardless of duration (13-16). At slightly higher levels, a small but definite percentage of the people thus exposed will become hearing-impaired, and that percentage will increase with increased exposure intensity. Since the risk of injury depends on the total sound energy of
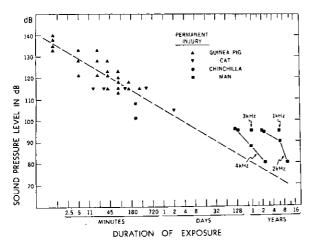
FIGURE 3. - Scatter plot of some combinations of levels and durations of noise exposures that have been shown to produce permanent injury. The parameters shown for man at 4, 3, 2 and 1 KHz treat threshold at each of these audiometric test frequencies separately. At a given level, it takes more time to produce threshold shifts at lower frequencies (12).

the noise exposure, the intensity of the exposure can be increased if the duration is lessened without changing the damage-risk. Thus, in a strictly physical sense, for every doubling of intensity which is equivalent to an increase of 3 dB(A) of sound energy (the decibel scale is logarithmic), the duration of exposure should be halved if the risk is to be kept the same. However, empirical data indicate a closer approximation of the ear's response to sound if the duration of exposure is halved for every 5 dB(A) increase in intensity.

In general, the frequency spectrum of the noise determines the location of maximal damage in the cochlea; the intensity and duration of the noise determines the severity of the damage. As the basal turn of the cochlea transduces high frequency sound into neural impulses and the apical turn the low frequencies, high frequency sound damages the basal turn and low frequency the apical turn. The frequencies of maximal loss are one-half to one octave above the exposure frequency.

The human ear is more sensitive to the damaging effects of high frequency sound than to low frequencies. This is because of the resonance characteristics of the external auditory canal which amplify high frequency sound of 4000 hertz (Hz) by as much as 18 dB. Also there is greater redundancy in hair cell distribution for the transduction of low frequency than for high frequency sounds (17). Twenty percent of the hair cells may be damaged in the apex with no change in hearing sensitivity. However, such damage in the basal turn results in approximately a 40 dB hearing loss. Low frequency sounds cause a diffuse pattern of stimulation of the basilar membrane, as the travelling wave starts in the basal turn and peaks at the apex. The travelling wave from high frequency sound is limited to a smaller region on the basal turn of the basilar membrane. Cellular loss from high frequency sound is reflected in a more profound loss of hearing sensitivity. Thus, for estimating damage risk of noise, a filter which attentuates the low frequencies to which the human ear is less sensitive, is used on the sound level meter, and exposure to the resulting A- weighted sound levels is well correlated with hearing impairment. For the above reasons, the hearing loss of industrial workers, who are mainly exposed to noise of a wide frequency range, centers at 4000 Hz and to produce a hearing loss in the lower frequencies of 1, 2, or 3 KHz, longer exposures are required as shown in Fig. 1.

The pathology of noise-induced hearing loss has been well characterized. Fig. 4 shows the outer hair cells in a normal organ of Corti as seen in a surface preparation, and Fig. 5 shows the hair cells as seen by the scanning electron microscope. The hair cells which are the final transducer of mechanical to neural energy are arranged in an orderly pattern of three rows of outer hair cells and one row of inner hair cells (18). Fig. 6 is a surface preparation of a noise-damaged organ of Corti for comparison with Fig. 4. The loss of the sequential pattern of hair cells is obvious and the degenerating or dead cells shown here can be noted by a cochleogram as in Fig. 7, which is an exact, cell for cell, reproducible diagram of the pathology. Here the pattern of cellular damage after noise exposure reveals a scat-
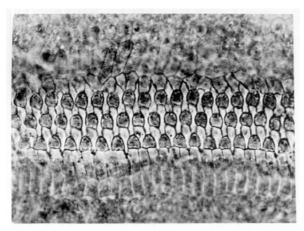
FIGURE 4. - Surface preparation of the organ of Corti from a squirrel monkey, obtained by microdissection of an osmium tetroxide fixed and stained cochlea, showing the very regular, geometric pattern of the three rows of outer hair cells. The one row of inner hair cells is above them but cannot be seen because it is out of the focal plane (18).

tered loss of outer hair cells involving all three rows equally. However, the sensory cells in the one-half and one and one-half turns from base are damaged more than in the apical turns. The increased susceptibility of the sensory cells of the basal turn accounts for the clinical observation that the hearing losses from industrial noise exposure center at around 4000 Hz. As we shall see, this type of damage is different from that due to the ototoxic antibiotics, where the loss begins in the outermost row of the outer hair cells at the basal turn, working its way to the apical turns. Electron microscopic observations of noise-exposed laboratory animals have demonstrated the early changes of degeneration of the organ of Corti. Work by Dr. David Lim (19) shows the appearance of vesicles along the surface of the stereocilia of the hair cells as the most subtle change after noise
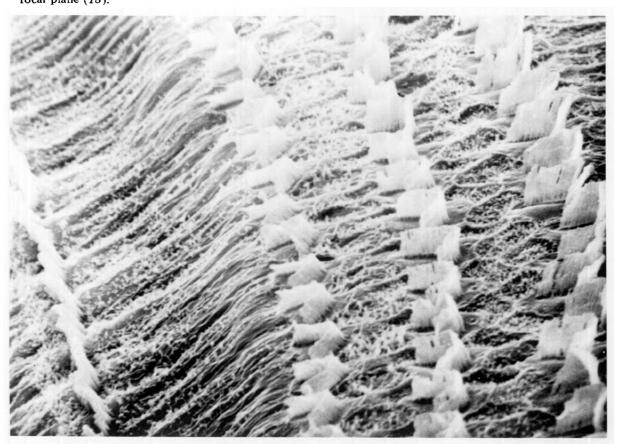

FIGURE 5. - Scanning electron micrograph of a normal guinea pig organ of Corti. The stereocilia of the outer hair cells are arranged in a W-shaped pattern while those on the inner hair cells line up in parallel rows (19).
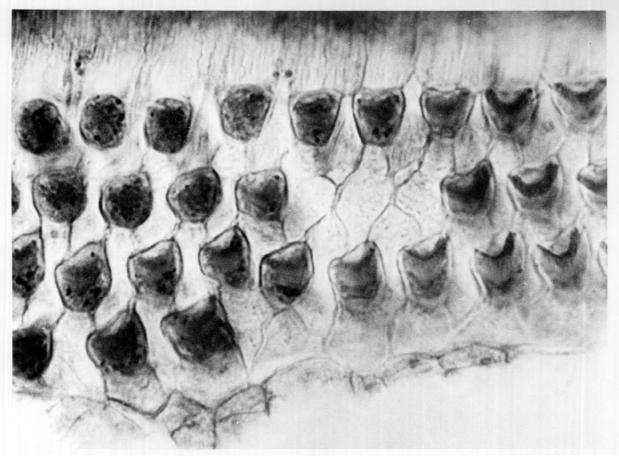
FIGURE 6. - Phase contrast micrograph of a surface preparation of a squirrel monkey organ of Corti, 1-1/2 coils from base, noise exposed. There were scattered cells lost in this region, and the micrograph shows the phalangeal scar replacing two destroyed cells. A normal variation is the presence of four rows of cells in the left third of the specimen. Magnification 1480X *(18)*.

exposure. (Fig. 8). As exposure continues, these vesicles rupture and the cytoplasm of the hair cells undergoes vesiculation leading to vacuolization (Fig. 9) *(19-22)*. There is an increase in the number of Hensen bodies *(20)*, a normal constituent of the outer hair cells. These are membranous structures which represent a specialized Golgi apparatus surrounded by mitochondria *(23)*. Vacuolization of the nuclear membrane, and subsurface and subsynaptic cisternae was also noted (Fig. 10). Softening of the cuticular plate (Fig. 11), which functions to support the stereocilia, follows and finally the hair cells become extremely swollen and degenerate (Fig. 12).

Pathological changes are not limited to the sensory cells but also occur in supporting cells (Dieter's) adjacent to them. These cells

undergo vacuolization *(19)* and their cellular junctions with other supporting cells (Hensen's) become disrupted *(22)*. Afferent *nerve endings whose mitochondria swell are* also affected *(19)*. Outer hair cells degenerate before the inner cells, followed by disappearance of the cochlear nerve fibers synapsing at the hair cells. *The final pathology of noise-induced ototoxicity is a completely denuded* organ of Corti which becomes replaced by a layer of simple epithelium.

But how does noise mediate these structural alterations? Unfortunately, knowledge of the physio-biochemical events in the normal hearing process is incomplete, let alone the events occurring with exposure to noise. Although the mechanisms of production of noise-induced hearing loss remain

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FIGURE 7. - Cochleograms showing the distribution of cellular damage in a guinea pig cochlea exposed to pink noise at 113 dB for 2 hours on each of three consecutive days. Each dark dot represents one damaged hair cell, a light dot represents a normal cell. The dots in toto comprise a cochleogram which is an exact cell for cell diagram of the pathology. Greatest damage occurs at 1/2 and 1 1/2 turns from the base (18).
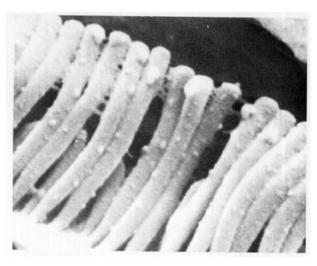

FIGURE 8. - Scanning electron micrograph of stereocilia from noise exposed animal. The earliest changes are the vesicles along the surface of the stereocilia. Initially the cytoplasmic membrane is intact but later ruptures (19).
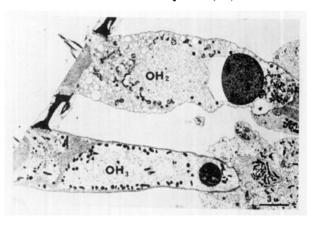

FIGURE 9. - Transmission electronmicrograph of vacuolated (OH_2) and moderately vesiculated (OH_3) outer hair cells of the second turn. Animal was exposed to noise of 117 dB SPL with octave bandwidth of 300 to 600 Hz for four hours (19).

obscure, present knowledge does suggest a few hypotheses. These include changes in the normal biochemistry and vasculature as mediators of the final damage.

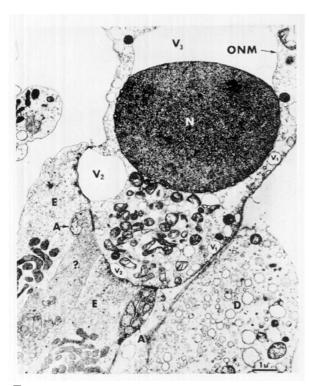From the above electron microscopic observations, the primary insult to the

FIGURE 10. - Transmission electronmicrograph of base of noise-damaged outer hair cell showing vacuole (V_3) formed by a dilated outer nuclear membrane (ONM), vacuoles (V_2) formed by dilated subsynaptic cisternae, and vacuole (V_1) formed by dilated subsurface cisternae. Afferent nerve ending (A) contains swollen mitochondria *compared to efferent (E) endings. The supporting* (Deiter, D.) cell also is vacuolated (*19*).

cochlea from noise is a generalized swelling of the smooth endoplasmic reticulum (consisting of subsurface and subsynaptic cisternae and Hensen's body) which functions as one interconnected system with the nuclear membrane (Fig. 2). It is hypothesized that ionic fluxes across this smooth ER complex are intimately involved in the transduction of mechanical stimulation (bending of stereocilia) to neural impulse initiation in the afferent endings of the auditory nerve. A reverse analogy can be made with the smooth ER in striated muscle (sarcoplasmic reticulum) which transduces neural impulses into mechanical contraction. (Neural impulses cause the sarcoplasmic reticulum to release calcium ions which activate ATPase resulting in contraction of the myofilaments.) Over-stimulation by noise damages first the smooth ER complex, most likely a crucial organelle in the transduction process.

Moving picture recordings of blood flow in the exposed vessels of the stria vascularis and spiral ligament have revealed that moderate noise levels of 90 dB (277 Hz) do not affect blood flow rate or vessel diameter. With exposures above 120 dB, blood flow rate increases with the sound intensity (*24*). The decrease in oxygen tension in the endolymph occurring with acoustic stimulation (*25, 26*) must reflect an increase in the rate of oxygen utilization by the cochlea to the point that utilization outstrips supply. Although noise causes an increase in the blood flow rate in the stria vascularis and spiral ligament, the spiral vessels of the basilar membrane (Fig. 2) which provide the direct oxygen supply to the organ of Corti (*27*) react differently and *undergo vasoconstriction (28)*. The consequent hypoxia leads to hair cell dysfunction and degeneration in short order. As these early biochemical and vascular lesions progress, an elevation of the hearing threshold occurs. Such a threshold shift is temporary if these changes are reversible. However, if the overstimulation continues, the changes progress to an irreversible lesion of cell degeneration and permanent threshold shift.

Drug-induced Ototoxicity

Ototoxic drugs fall into three groups—salicylates and quinine, potent diuretics, and antibiotics. Tinnitus or ringing in the ears and hearing loss, the classical symptoms of salicylism and cinchonism, attest to the long-known ototoxicity of salicylates and quinine. Burnett's *Treatise on the Ear* (1884) (*29*) acknowledges the effects of these drugs and suggests their mechanism " . . . both salicylic acid and quinine produce hardness of hearing . . . and may produce permanent changes in the ear by vaso-motor disturbances." Our present understanding of the mechanism is only slightly more sophisticated. Hawkins (*30*) has demonstrated vasoconstriction in the stria vascularis and
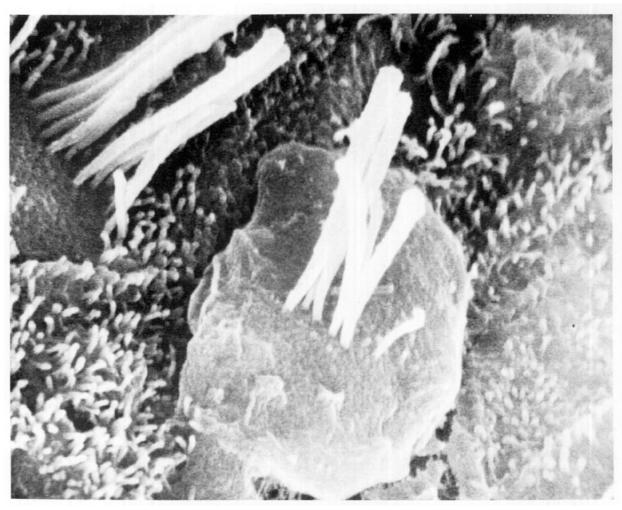
FIGURE 11. - Scanning electron micrograph of swollen cuticular plate of outer hair cell. The cuticular plate is the topmost part of the hair cell and provides attachment for the stereocilia. Animal was exposed to 117 dB SPL, 300-600 Hz bandwidth for 16 hours (19).

incomplete blockage of spiral vessels in the basilar membrane in guinea pigs after sodium salicylate administration and has inferred that the resulting ischemia impairs cochlea function. Daily doses of 6 - 8 grams of salicylates as are used in patients with arthritis and collagen-vascular diseases produce a bilateral sensorineural loss of 20-40 dB affecting all frequencies and fortunately completely reversible within days after cessation of therapy (31, 32). This hearing loss has been localized as intracochlear by the use of differential audiometry (33). Quinine usually produces a similar reversible hearing loss by causing partial blockage of the spiral vessels beneath the basilar membrane by swollen

endothelial cells (30). Continued therapy can lead to permanent losses by causing degeneration of the spiral ganglion cells and the myelin sheath of the auditory nerve (34). Studies of pathology of the organ of Corti resulting from these agents have produced conflicting results. Acute administration of salicylates and quinine produce degeneration and collapse of the organ of Corti (35), and chronic treatment with salicylates produces mitochondrial pathology in hair cells (36) In other hands, no consistent light or electron microscopic changes were identified in the organ of Corti (30, 37).

Since 1966, clinical use of the potent diuretics, ethacrynic acid and furosemide, has
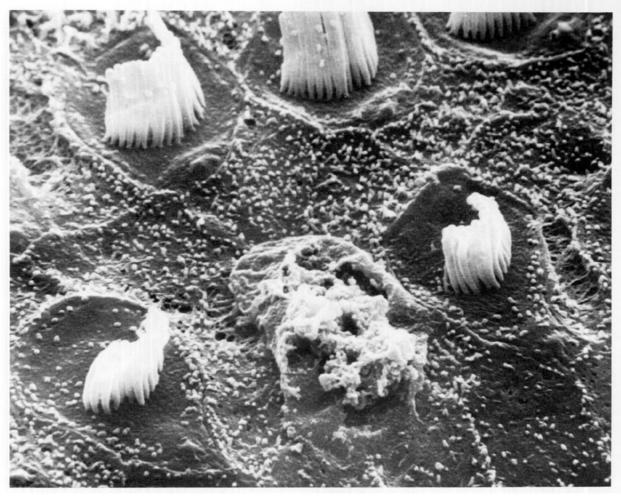
FIGURE 12. - Scanning electron micrograph of a degenerated outer hair cell among normals. Exposure was with 117 dB SPL, 1-2 kHz bandwidth for 14 hours *(19)*.

brought attention to their ability to produce bilateral sensorineural hearing loss. One-third of an intravenous dose of ethacrynic acid is excreted by the liver into the bile and two-thirds is excreted by the kidney. With normal renal and hepatic function, elimination of the drug is so rapid that accumulation does not occur despite repeated administration *(38)*. Because of the reduced excretion of the drug, the hearing loss occurs in patients with hepatic or renal impairment. Ethacrynic acid has produced a reversible hearing loss in the presence of chronic liver disease *(39)* and permanent deafness in the presence of both cirrhosis and renal failure *(40)*. In the presence of uremia, the hearing loss is acute in onset, usually transient *(41, 42, 43)*, and can be initiated by normal oral dosage of the drug

(41), although usually large intravenous doses were used. However, permanent deafness in the setting of renal failure does occur *(44)*. Likewise, high doses of intravenous furosemide (2000 - 5000 mg) used in patients with diminished renal function secondary to chronic and acute renal failure and post-renal transplant anuria produce acute transient sensorineural deafness *(45)*.

In clinical dosage (1 mg/kg body weight) ethacrynic acid exerts a profound effect on the electrolyte composition of the endolymph *(46)* (the fluid filling the membranous labyrinth which is surrounded by perilymph). The normal intracellular-like composition of endolymph (Na 5.9 mEq/L, K 145 mEq/L) is reversed and contains Na 143 mEq/L and K 21.0 mEq/L just 10 minutes after ethacrynic

acid administration. The normal extra-cellular-like composition of the perilymph (high Na, low K) remains unaffected. Clearly, ion transport and/or permeability of the cochlear membranes such as Reissner's membrane, stria vascularis or the cochlear partition (organ of Corti and the basilar membrane) are exquisitely sensitive to ethacrynic acid, which has been shown to inhibit Na-K activated ATPase (47). Less sensitive to ethacrynic acid are the cochlear microphonic and auditory nerve action potential which undergo a reduction in amplitude with doses of 10 mg/kg. Complete recovery within 1 hour is the rule, but a second dose of ethacrynic acid produces a greater amplitude reduction and recovery then requires days (48). Various pathological changes occur with ethacrynic acid from atrophy of cells of stria vascularis (49) to destruction of outer hair cells in the basal and middle turns of the cochlea (48).

Although the aminoglycosidic antibiotics including streptomycin, kanamycin, neomycin, and gentamicin have proved very effective in the chemotherapy of tuberculosis and Gram negative infections, their ototoxicity has been a significant problem with their use. The characteristics of the well studied toxicity of kanamycin (50-53) serve as an example for the other antibiotics. Hearing loss from this drug, heralded by tinnitus, is of the sensorineural type with both bilateral and unilateral involvement although the former is more often observed. The hearing loss is usually reversible in the very early stages if the drug is discontinued but becomes permanent with prolonged administration. Upon audiometric evaluation high frequency losses (4000-8000 cps) are more often present than losses in the low, speech frequencies (500-2000 cps) used in conversation. There is a wide range in the severity of hearing losses from a few to more than 40 decibels. The development of ototoxicity directly correlates with the dose of the drug—both total dose and average daily dose—, with length of treatment, and with the presence of impaired renal function often initiated or exacerbated by the kanamycin itself. As kanamycin is excreted almost exclusively by glomerular

filtration (38), blood levels are elevated and high levels are prolonged in patients with renal disease (54), thus predisposing these patients to ototoxicity. Similarly, patients with diabetes mellitus, although not having elevated serum creatinine and blood urea nitrogen, may have enough impairment of glomerular filtration to be predisposed to kanamycin ototoxicity. Patients over 45 years of age develop ototoxicity more frequently and more severely than do younger patients and the presence of sensorineural losses from recent administration of other ototoxic antibiotics potentiates the hearing loss from kanamycin (55).

Studies of the kinetics of the aminoglycosidic antibiotics in plasma and inner ear fluids have helped explain the observed clinical ototoxicity. After intramuscular injection peak plasma levels of the antibiotics occur in 1-2 hours and none of the drugs is detectable in the blood 24 hours after administration (38). Uptake and excretion of the drugs in the inner ear fluids are more slowly accomplished (56-59). Peak levels in perilymph occur 4 hours after injection. There is a linear relation between the dose of kanamycin and its concentration in plasma. In contrast, the kanamycin concentration in the perilymph increases by a factor of ten (from 2 to 20 μg/ml) with a doubling of dosage (25 to 50 mg/kg). Thus, small increases in clinical dosages magnify the risk of ototoxicity. Approximately 10% of the peak perilymph concentration of kanamycin remains after 24 hours while about 65% of neomycin remains. Not until 55 hours after injection of neomycin are unmeasurable traces found. Because of such slow excretion, daily kanamycin and neomycin injections result in successively higher perilymph concentrations. Excretion of the antibiotics correlates well with their ototoxicity: neomycin is most slowly eliminated and is most ototoxic while streptomycin, completely excreted after 24 hours, is the least toxic.

Antibiotics administered by nonparenteral routes can also be ototoxic. Hearing losses in patients can occur when streptomycin is applied locally in the form of ear drops for

chronic otitis media (60). Direct intra-tympanic application of neomycin, poly-myxin B, and colimycin causes cellular damage to guinea pig cochleas (61). The drugs reach the inner ear fluid spaces from the middle ear probably by diffusion through the round window membrane and the annular ligament around the stapes footplate. Although poorly absorbed from the gastrointestinal tract, neomycin can be systemically absorbed when used in large doses for bowel sterilization prior to surgery. Deafness can occur from neomycin given orally (62) or by colonic irrigation (63) and also after intrapleural instillation (64).

Histological observations of antibiotic treated laboratory animals and humans reveal a systematic and sequential pattern of degeneration in cellular and neural components of the inner ear (65-68, 18) (Fig. 13). Initial

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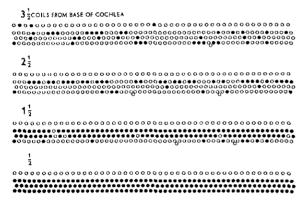●●

FIGURE 13. - Cochleogram of guinea pig treated with framycetin 200 mg/kg body weight for 8 consecutive days showing the systematic pattern of hair cell damage. Outer hair cells in the basal coil are completely destroyed with damage decreasing toward the apex (18).

pathological changes occur in the first row of outer hair cells in the organ of Corti in the basal turn of the cochlea. With increasing dosage, changes involve all three rows of the outer hair cells in the basal turn and the first row in turns 1 1/2 and 2 1/2 from the cochlear base. Cells in the second and third rows in these turns will become damaged later. When outer hair cells in the apex of the cochlea become involved, all rows of the basal turn are completely degenerated. Thus,

destruction of outer hair cells begins in the basal turn and extends toward the apex. Destruction of the inner hair cells, however, occurs after damage to the outers has begun in the apical turn, and extends from the apex to the base. Nerve endings and fibers supplying the sensory cells degenerate after the latter (69). The normal chalice-like neural endings are lost and the complex neural network clumps. The sequential pattern of sensory cell degeneration corresponds to the distribution of endings of the efferent nerves which originate at the superior olivary complex in the brain stem and terminate on the sensory cells. Whether this efferent system is instrumental in inducing antibiotic toxicity is an interesting hypothesis.

The increased susceptibility of the sensory cells of the basal turn to antibiotics accounts for the clinical observation that hearing losses involve high frequencies earlier, more commonly, and more severely than low frequencies. Hearing losses in the latter do occur, but usually only after the high frequencies are profoundly affected.

Early pathological changes in the hair cells as observed by the electron microscope involve the stereocilia and mitochondria (70, 71). The "W" pattern of the former becomes disorganized, swells, clumps and finally disapppears. The mitochondria above the nucleus swell, their membranes disintegrate and become filled with myelin figures. The cuticle into which the stereocilia lie deteriorate, the cell membrane collapses and cytoplasm is extruded from the cell. These changes result in the collapsed cells as seen by light microscopy (38, 69) (Fig. 14).

Ototoxicity of noise and drug in combination

Research into the effects of noise and drugs in combination is limited, but the preliminary literature strongly points to one conclusion—that of potentiation of separate damaging effects. I would like to review each of these studies as they are the only documented and factual information available to us.

Dayal et al. in a well controlled study (72) exposed guinea pigs to continuous noise and
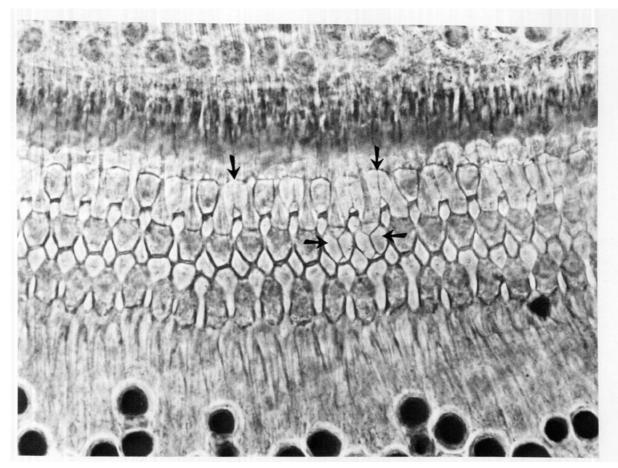
FIGURE 14. - Phase contrast micrograph of organ of Corti, 2-1/2 coils from base, from a guinea pig injected with kanamycin 400 mg/kg/day for eight days. Note the typical spider-like appearance of the collapsed cells (arrows). Ten such cells are present in the first (upper) row and two in the middle row. The third row is normal. Magnification 735X *(18)*.

to daily injections of kanamycin. The source of the noise was a pediatric incubator which produced levels of 68 to 72 dB at predominantly 125 Hz. Animals exposed to this noise alone for five weeks developed a small degree of damage to the outer row of OHC in apical turns as assessed by light microscopic evaluation of surface preparations of the organ of Corti. Daily treatment with kanamycin for 5 weeks at 15 or 50 mg/kg did not produce any discernible damage. However, when both influences were applied for 5 weeks, the groups receiving noise and kanamycin at doses of 15 and 50 mg/kg suffered a twofold and fourfold loss respectively of outer hair cells compared to the noise-only treated animals. These investigators also showed that hair cell damage can occur after a shorter interval of

exposure (3 weeks) to a larger dose of kanamycin (100 mg/kg) and to the incubator noise, each influence alone causing no injury. They concluded that low level noise sensitizes the cochlear hair cell to damage by kanamycin.

Quante (73) performed experiments similar to those of Dayal but using larger doses of kanamycin and more intense noise, their results are more striking. They assessed cell death or damage by similar surface preparations of the guinea pig organ of Corti after 8 days exposure to kanamycin (250 mg/kg), pink noise characterized by equal intensity in a wide frequency distribution (80 to 10,000 Hz), and to both agents. The kanamycin alone and the noise at 90 dB alone failed to produce morphologic changes. However, both agents

applied together damaged approximately 67% of the outer hair cells in the first half turn of the cochlea, 78% in the second, 33% in the third and 11% in the fourth. With exposure to 100 dB noise and kanamycin, an average of 65% of the outer hair cells were found injured compared to 5% and negligible damage upon exposure to noise and kanamycin respectively. A similar striking result was seen secondary to 110 dB sound and kanamycin insults. Quante et al., concluded that synergistic damage resulted from combined kanamycin and sound exposure.

Using a .32 caliber pistol as a source for noise exposure and kanamycin, cochlear damage was more extensive in guinea pigs which had received the drug and noise than upon exposure to either agent along (74). A unique type of exposure to noise and antibiotics occurs when a patient on long-term antibiotic therapy undergoes ear surgery and is exposed to noise from the procedure itself. Attention to this problem revealed that when noise is applied after kanamycin, a synergistic damage occurs but not so when noise is applied before. In this case, damage was similar to that resulting from the antibiotic alone (75). Injection of a wide range of drugs-chenopodium oil, quinine, salicylic acid or dihydromycin—prior to noise exposure enhances the damage from the latter (76).

All the above studies confirm that the administration of ototoxic drugs produces an increased susceptibility to noise damage. Levels of noise which by themselves are benign cause damage in the presence of known ototoxic drugs. According to the Dayal study levels of 68 to 72 dB, which are 10 dB less than those considered unsafe, are damaging in the presence of drugs. Although many types of drug-noise interactions need to be investigated in the laboratory and clinic, these studies raise the possibility that occult inner ear damage is occurring in many people exposed to low levels of both agents. Presbycusis, the hearing loss associated with advancing age, may partly be the result of repeated episodes of such occult damage. Simultaneous exposure can be coincidental or related as when aspirin is ingested to relieve a tension headache caused or exacerbated by noise.

Theoretical Considerations

Our present concepts of pathophysiology of hearing loss from noise and drugs permit speculation of mechanisms for potentiation.

Noise, quinine and salicylates each produce vasoconstriction of spiral vessels in the basilar membrane which supply oxygen to the organ of Corti. A more severe vasoconstriction and anoxia may result from a combination of the agents. Salicylates also produce vasoconstriction in the stria vascularis, which maintains the high positive (+80 mV) endocochlear potential. The latter is necessary for generation of cochlear microphonics, a reflection of hair cell activity, and is extremely sensitive to anoxia (77). Salicylates decrease the magnitude of the cochlear microphonics (78) and may accomplish this by their hypoxic effect on the stria vascularis and consequent depression of the endocochlear potential.

Noise and ethacrynic acid may have common pathways for interaction by their effects on membrane permeability. Noise causes swelling of the smooth ER complex and ethacrynic acid, known to inhibit Na-K-activated ATPase which provides energy for active transport, causes reversal of Na and K concentrations in the endolymph. The aminoglycosidic antibiotics are well recognized inhibitors of protein synthesis. Streptomycin prevents amino-acyl-t-RNA complexes from attaching to their proper codons on m-RNA thereby preventing translation. The consequent deficiency of necessary enzymes and structural proteins for cell repair may produce early stages of cochlear dysfunction.

Since transduction of auditory stimuli to neural impulses is an energy requiring process, noise may place extra demands on the energy supplying system of the hair cells. Ethacrynic acid inhibits glycolysis (79, 80) and salicylates uncouple oxidative phosphorylation. Thus, drugs may limit the energy supply, the demands for which are increased during noise exposure.

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